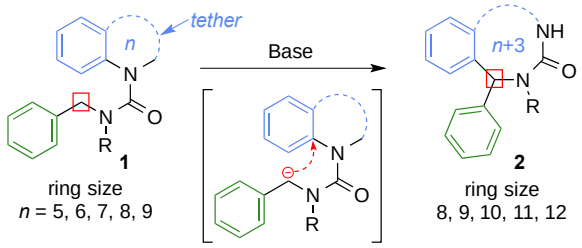
# Medium Ring Nitrogen Heterocycles by Migratory Ring Expansion of Metallated Ureas

Jessica E. Hall[a], Johnathan V. Matlock[a], John W. Ward[a], Katharine V. Gray[b] and Jonathan Clayden*[a]

**Abstract:** Simple benzo-fused nitrogen heterocycles (indolines, tetrahydroquinolines and their homologues) undergo migratory ring expansion by deprotonation of their benzylic urea derivatives with LDA in the presence of DMPU. The products of the reactions are benzodiazepines, benzodiazocines and their homologues, with ring sizes of 8-12. The reactions tolerate a range of substituent patterns and types, and may exhibit enantiospecificity or diastereoselectivity. Considerable complexity is rapidly generated in an efficient synthesis of these otherwise difficult to obtain medium-ring nitrogen heterocycles.

Medium-ring (8 to 12-membered) heterocycles are a class of challenging synthetic targets.[1] Natural products containing medium ring N and O heterocycles and exhibit a broad range of biological activities,[2] so the scarcity of 8 to 12-membered rings among approved pharmaceutically active agents[3] is surprising, and indicative of the acknowledged difficulties associated with their synthesis.[4] Over 80% of drugs contain nitrogen heterocycles of four to seven members,[3] with benzodiazepines constituting a particularly privileged structure.[5] Larger heterocyclic rings are likewise prevalent in biologically active macrolides[6] and cyclic peptides.[7] Recent exploration of drug candidates containing medium ring nitrogen heterocycles,[8] has highlighted the importance of conformational constraints in these structures.[9] Methodology allowing the straightforward synthesis of classes of nitrogen heterocycles with ring sizes of eight or more would prove particularly valuable for exploring this less charted area of chemical space.

In this paper we report a method for the synthesis of medium ring (8 to 12-membered) benzo-fused nitrogen-containing heterocycles by $n \rightarrow n+3$ ring expansion of readily available heterocyclic precursors. The method is summarised in Scheme 1, and builds on our studies of stereospecific N to C migration of aryl rings within metallated ureas.[10] By analogy with this previous work, we expect selective deprotonation of the highlighted position $\alpha$ to nitrogen in ureas **1** to give the anion shown (or its organolithium equivalent). Such anions, in the absence of a 'tether', undergo nucleophilic attack on the *N*-aryl substituent shown in blue, and with a cyclic substrate we would expect consequent migratory ring expansion of the *n*-membered ring of **1** to the *n*+3 membered product **2**. The ready availability of 5-7 membered heterocyclic precursors makes this a particularly appealing route for the synthesis of the 8-10 membered products.




***Scheme 1***. Migratory ring expansion of metallated ureas.

Preliminary investigations (Table 1) employed as a model substrate the urea **3a**, available in two steps from commercially available indoline. Deprotonation of **3a** with either freshly prepared lithium diisopropylamide (LDA) or *sec*-butyllithium did not lead to ring expansion. Instead, a 1,2-acyl shift, resulting from attack of the benzylic anion onto the urea carbonyl group generated the aminoamide **5** (Table 1, entries 1 and 2).[11] Since *sec*-BuLi also gave alkylated by-products[10d] as a consequence of nucleophilic attack on the urea, LDA was used as the base in all subsequent reactions.

*N*,*N*'-Dimethylpropylideneurea (DMPU) can dramatically alter reaction pathways of organolithium species in solution when used as a ligand or co-solvent.[10f, 12] Significantly, treatment of **3a** with LDA in the presence of DMPU suppressed completely the acyl shift leading to **5** and gave instead the ring expanded benzodiazocine **4a** in good yield (Table 1, entry 4). An even higher yield of benzodiazocine **4b** was obtained with the 5-chloroindoline-derived urea **3b** (entry 5).

***Table 1***. Optimisation of the ring expansion.

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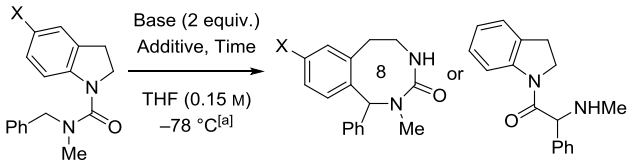



**3a** (X = H)
**3b** (X = Cl)

**4a** (X = H)
**4b** (X = Cl)

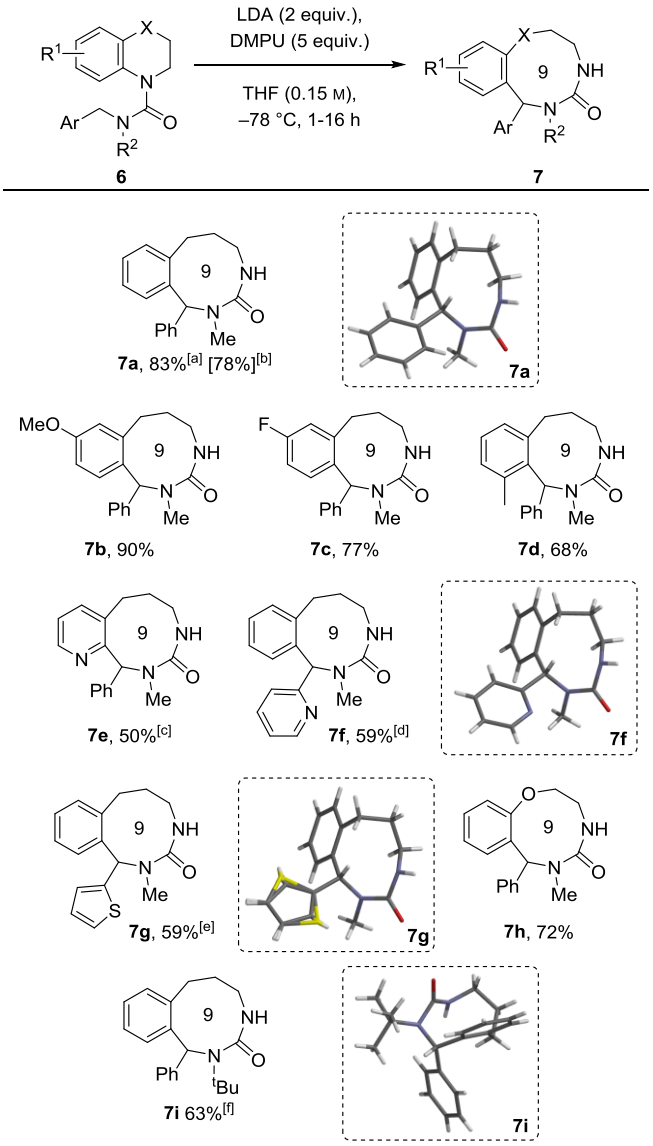
**5**

| Entry | S.M. | Base | Additive | Time (h) | Product, Yield (%) |
|---|---|---|---|---|---|
| 1 | **3a** | LDA[b] | - | 4 | **5** 66 |
| 2 | **3a** | *sec*-BuLi | - | 2 | **5** 62[c] |
| 3 | **3a** | *sec*-BuLi | - | 4 | **5** 12[c] |
| 4 | **3a** | LDA | DMPU (5 equiv.)[d] | 4 | **4a** 68[b], 70[e] |
| 5 | **3b** | LDA[e] | DMPU (5 equiv.)[d] | 4 | **4b** 88 |

[a] Optimisation carried out on 0.38 mmol scale. [b] LDA freshly prepared by treatment of anhydrous diisopropylamine with *n*-BuLi at -78 °C in THF. [c] $^1$H NMR showed side-products resulting from the addition of *sec*-BuLi to both **3a** and **4a**. [d] DMPU was added to a solution of **3a** in THF at RT prior to cooling to -78 °C to ensure effective mixing. [e] Commercially sourced LDA purchased from Sigma Aldrich as a 2.0 M solution in THF/heptane/ethylbenzene. LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5-6-tetrahydro-2(1*H*)-pyrimidinone.

These conditions (LDA, 2 equiv.; DMPU, 5 equiv.; THF, –78 °C, 1-16 h) were applied successfully to a series of ureas **6a-i** derived from commercially available 6-membered heterocycles, and allowed the synthesis of a range of substituted 9-membered benzodiazonines **7a-j** in good to excellent yield (Scheme 2). Ring-expansion of **6a** generated **7a** in good yield on a scale of both 0.4 mmol and 3 mmol, with X-ray crystallography confirming the benzodiazonine structure of **7a**. The ring-expansion reaction is insensitive to both electronic or steric demands, giving the ring expansion products with electronically diverse (**7b, 7c**) and *ortho*-substituted hindered (**7d**) migrating substituents in good to excellent yields.

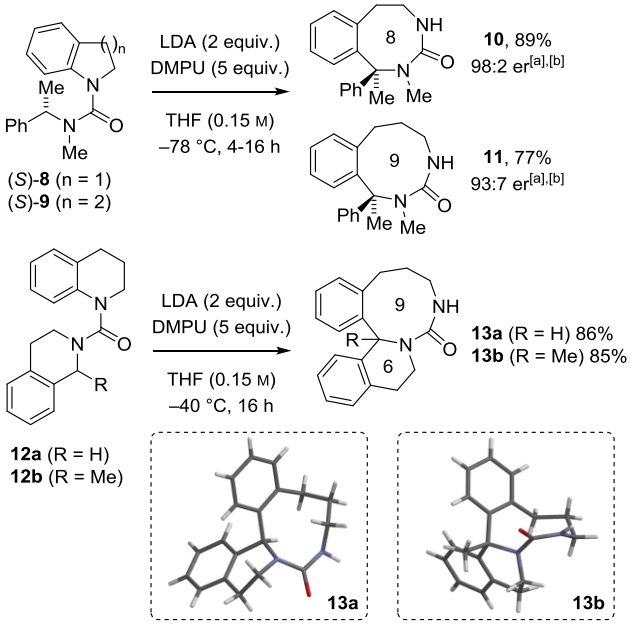
Heteroaromatic (2-pyridyl and 2-thiophenyl) rings may be incorporated into the migrating aryl ring (**7e**) or α to the benzylic anions (**7f**, **7g**). Higher temperatures are required for the reactions of pyridyl-containing substrates to reach completion. By contrast, the 2-thiophenyl-stabilised anion derived from **6g** rearranged successfully to **7g** even in the absence of DMPU. Incorporation of a heteroatom into the tether by expansion of a urea **6h** derived from commercially available benzomorpholine gave the benzoxadiazonine **7h**. Replacing the *N*-methyl substituent with a *tert*-butyl group substantially decreased the rate of the reaction of **6i**, which required an elevated temperature to obtain a good yield of the ring expansion product **7i**.



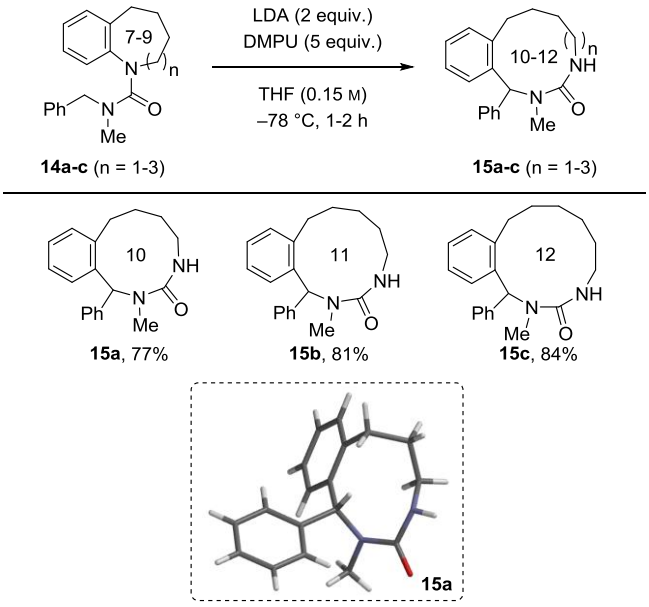

**6** **7**

***Scheme 2***. Ring expansions to yield 9-membered nitrogen heterocycles. [a] Yield in parenthesis: reaction conducted on 0.4 mmol scale. [b] Yield in parenthesis: reaction conducted on 3 mmol scale. [c] Reaction run at −60 °C. [d] Reaction run at −30 °C. [e] Reaction run at −40 °C without DMPU. [f] Reaction run at −10 °C.

Chiral substrates **8** and **9** were made from enantiopure (*S*)-α-methylbenzylamine and were ring-expanded under the same conditions (Scheme 3). Each gave a product, **10** and **11**, with a new quaternary centre within the expanded 8- or 9-membered ring. Both rearrangements were stereospecific, with only slight erosion of e.r. in the case of **11**, and must proceed through a configurationally stable organolithium intermediate.[13]



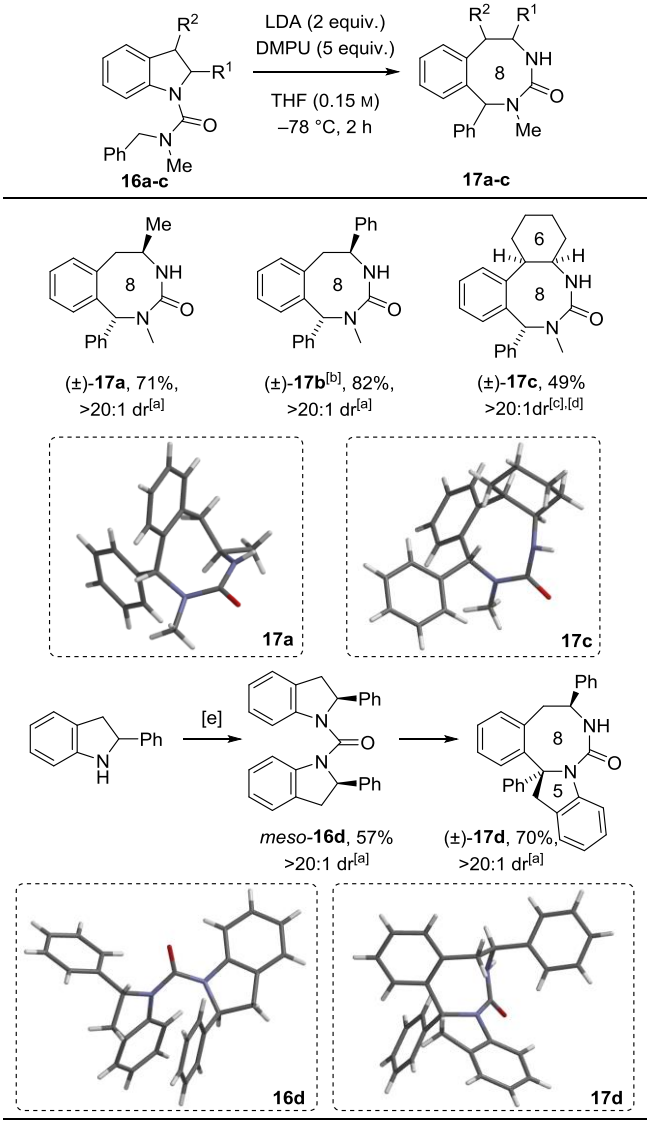

***Scheme 3***. Ring expansion products with quaternary centres and fused rings. [a] e.r. determined by HPLC on chiral stationary phase. [b] Starting material (*S*)-**8** (99:1 e.r.), (*S*)-**9** (99:1 e.r.).




***Scheme 4***. Migratory ring expansion to 10-12 membered rings.

The methodology was also amenable to the synthesis of bicyclic structures by migratory ring fusion (Scheme 3). The unsymmetrical ureas **12**, formed by coupling two isomeric 6-membered nitrogen heterocycles, underwent ring expansion by insertion of the tetrahydroisoquinoline ring into the tetrahydroquinoline. The diazabicyclo[7.4.0]tetradecane products **13a** and **13b** were formed at –40 °C in excellent yield, highlighting the way that structural complexity is rapidly generated from the simple urea precursor.

Having made 8- and 9-membered heterocycles in just two or three steps from commercially available 5- and 6-membered precursors, we extended the ring expansion method to larger ring sizes (Scheme 4). The requisite 7-, 8- and 9-membered ureas **14** were made either from a commercially available precursor (**14a**, two steps from benzazepine) or by using literature procedures (**14b** and **14c**[14]). All three ureas underwent ring expansion to give 10-, 11- and 12-membered heterocycles in good yields.[15]

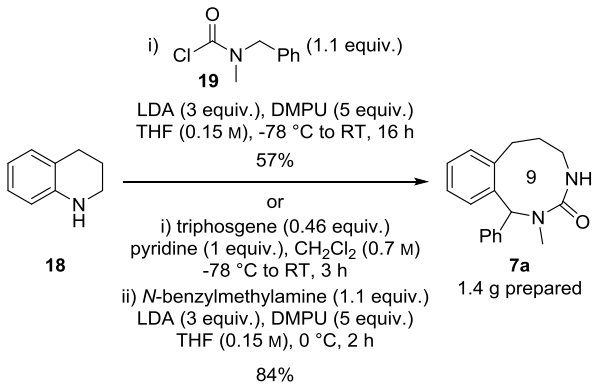



***Scheme 5***. Diastereoselective ring expansions. [a] dr was determined by $^1$H NMR of the crude reaction mixture. [b] The relative chemistry of (±)-**17b** was assigned in analogy to (±)-**17a**. [c] dr of purified product. [d] Reaction run without DMPU. [e] Reaction conditions: Triphosgene (1.2 mmol) treated with pyridine (2.6 mmol) in anhydrous $CH_2Cl_2$ (0.7 M) at −78 °C. 2-Phenylindoline (2.6 mmol) added and reaction warmed to RT. 2-Phenylindolinecarbamoyl chloride (0.78 mmol) treated with 2-phenylindoline (1.0 mmol) and triethylamine (1.24 mmol) in anhydrous MeCN (0.4 M) at RT.

Chiral starting materials with substituents in the expanding ring underwent migratory ring expansion with complete diastereoselectivity (Scheme 5). 2-Substituted indolines, prepared from the corresponding 2-substituted indoles,[16] were converted into the starting ureas **16**. Ring-expansion of methyl-substituted **16a** gave **17a** in good yields and as a single diastereoisomer. X-ray crystallography showed an 1,5-*anti* relationship between the two ring substituents, and indicated that both occupied pseudoequatorial positions on the chair-chair conformer of the eight-membered ring.[17] The related substrates **16b**-**c** also underwent ring expansion to single diastereoisomers of the eight-membered products.

A fourth indoline-derived substrate **16d** was formed by coupling of racemic 2-phenylindoline with its own carbamoyl chloride derivative. Remarkably, a single diastereoisomer of the symmetrical urea was formed, which X-ray crystallography showed to be the *meso* diastereoisomer. Migratory ring-fusion of this urea allowed one indoline ring to insert into the other, and gave diazabicyclo[6.3.0]undecane **17d** as a single diastereoisomer, with the *anti* relationship of the two phenyl rings determined by X-ray crystallography (Scheme 5).[18]

A particularly appealing feature of this migratory ring expansion is the ready availability of the starting materials, most of which are formed in two or three steps from commercial products. However, the practicality of the method can be increased even further by carrying out the urea formation and ring expansion as part of a single transformation (Scheme 6). Tetrahydroquinoline **18** can be ring expanded to the benzodiazonine **7a** in a single step by treatment with **19** and LDA (3 equiv.) in THF (0.15 M)/DMPU (5 equiv.) in moderate yield. An improved yield could be obtained by treatment of **18** with triphosgene/pyridine followed by *in situ* urea formation with *N*-benzylmethylamine and LDA (3 equiv.) to give **7a** in 84% yield on a gram scale.




***Scheme 6***. Telescoped ring expansion.

In conclusion, this new method provides synthetic tools to form, rapidly and efficiently, medium ring nitrogen-containing heterocycles with a range of benzo-fused cyclic urea structures. The compounds formed by the method exhibit substantial structural diversity, and occupy a skeletally novel and hitherto unexplored region of chemical space.

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**Keywords:** Medium Rings • Heterocycles • Migration • Ring Expansion • Organolithium •

[1] G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95-102.

[2] A. Hussain, S. K. Yousuf, D. Mukherjee, *RSC Adv.* **2014**, *4*, 43241-43257 and references cited therein.

[3] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.

[4] Selected methods for the synthesis of medium-sized rings a) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 3529-3533; b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963-3008; c) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, B. Roy, *Tetrahedron* **2007**, *63*, 3919-3952; d) T. P. Majhi, B. Achari, P. Chattopadhyay, *Heterocycles* **2007**, *71*, 1011-1052; e) M. J. Begley, L. Crombie, D. Haigh, R. C. F. Jones, S. Osborne, R. A. B. Webster, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2027-2046; f) W. Zhao, H. Qian, Z. Li, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 10005-10008; *Angew. Chem.* **2015**, *127*, 10143-10146. g) H. Braunschweig, I. Krummenacher, L. Mailander, F. Rauch, *Chem. Commun.* **2015**, *51*, 14513-14515; h) Z. Li, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Eur. J. Org. Chem.* **2014**, 2084-2091; i) G. Kulsi, A. Ghorai, P. Chattopadhyay, *Tetrahedron Lett.* **2012**, *53*, 3619-3622; j) K. C. Majumdar, K. Ray, S. Ganai, *Tetrahedron Lett.* **2010**, *51*, 1736-1738; k) K. C. Majumdar, *RSC Adv.* **2011**, *1*, 1152-1170; l) Á. Gyömöre, A. Csámpai, T. Holzbauer, M. Czugler, *Tetrahedron* **2011**, *67*, 2979-2990; m) R. A. Bauer, T. A. Wenderski, D. S. Tan, *Nat. Chem. Biol.* **2013**, *9*, 21-29; n) T. M. A. Barlow, M. Jida, K. Guillemyn, D. Tourwe, V. Caveliers, S. Ballet, *Org. Biomol. Chem.* **2016**, *14*, 4669-4677.

[5] a) G. A. Archer, L. H. Sternbach, *Chem. Rev.* **1968**, *68*, 747-784; b) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347-361; c) L. H. Sternbach, *J. Med. Chem.* **1979**, *22*, 1-7; d) C. D. Duarte, E. J. Barreiro, C. A. M. Fraga, *Mini-Rev. Med. Chem.* **2007**, *7*, 1108-1119.

[6] a) S. Omura, *Macrolide Antibiotics: Chemistry, Biology, and Practice*, Elsevier Science, **2002**; b) R. D. Norcross, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041-2114.

[7] R. M. J. Liskamp, D. T. S. Rijkers, S. E. Bakker, in *Modern Supramolecular Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, **2008**, pp. 1-27.

[8] a) J. Elleraas, J. Ewanicki, T. W. Johnson, N. W. Sach, M. R. Collins, P. F. Richardson, *Angew. Chem. Int. Ed.* **2016**, *55*, 3590-3595; *Angew. Chem.* **2016**, *128*, 3654-3659. b) P. Ventosa-Andrés, A. La-Venia, C. A. B. Ripoll, L. Hradilová, V. Krchňák, *Chem. Eur. J.* **2015**, *21*, 13112-13119; c) A. F. de la Torre, D. G. Rivera, O. Concepción, R. Echemendia, A. G. Correa, M. W. Paixão, *J. Org. Chem.* **2016**, *81*, 803-809; d) N. D.

P. Atmuri, W. D. Lubell, *J. Org. Chem.* **2015**, *80*, 4904-4918; e) L. Huang, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138*, 5793-5796; f) R. Doveston, S. Marsden, A. Nelson, *Drug Discovery Today* **2014**, *19*, 813-819.

[9] J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398-6401; *Angew. Chem.* **2009**, *121*, 6516-6520.

[10] a) J. Clayden, J. Dufour, D. M. Grainger, M. Helliwell, *J. Am. Chem. Soc.* **2007**, *129*, 7488-7489; b) J. Clayden, U. Hennecke, *Org. Lett.* **2008**, *10*, 3567-3570; c) R. Bach, J. Clayden, U. Hennecke, *Synlett* **2009**, 421-424; d) D. J. Tetlow, U. Hennecke, J. Raftery, M. J. Waring, D. S. Clarke, J. Clayden, *Org. Lett.* **2010**, *12*, 5442-5445; e) D. M. Grainger, A. Campbell Smith, M. A. Vincent, I. H. Hillier, A. E. H. Wheatley, J. Clayden, *Eur. J. Org. Chem.* **2012**, 731-743; f) M. Tait, M. Donnard, A. Minassi, J. Lefranc, B. Bechi, G. Carbone, P. O'Brien, J. Clayden, *Org. Lett.* **2013**, *15*, 34-37; g) D. J. Tetlow, M. A. Vincent, I. H. Hillier, J. Clayden, *Chem. Commun.* **2013**, *49*, 1548-1550; h) M. B. Tait, S. Butterworth, J. Clayden, *Org. Lett.* **2015**, *17*, 1236-1239; i) J. Maury, J. Clayden, *J. Org. Chem.* **2015**, *80*, 10757-10768; j) R. C. Atkinson, D. J. Leonard, J. Maury, D. Castagnolo, N. Volz, J. Clayden, *Chem. Commun.* **2013**, *49*, 9734-9736; k) R. C. Atkinson, F. Fernández-Nieto, J. Mas Roselló, J. Clayden, *Angew. Chem. Int. Ed.* **2015**, *54*, 8961-8965; *Angew. Chem.* **2015**, *127*, 9089-9093.

[11] For related rerrangements of lithiated carbamates see a) P. Zhang, R. E. Gawley, *J. Org. Chem.* **1993**, *58*, 3223-3224; b) S. Superchi, N. Sotomayor, G. Miao, B. Joseph, M. G. Campbell, V. Snieckus, *Tetrahedron Lett.* **1996**, *37*, 6061-6064; c) G. B. C. A. Slana, M. S. de Azevedo, R. S. C. Lopes, C. C. Lopes, J. N. Cardoso, *Beilstein J. Org. Chem.* **2006**, *2*, 1.

[12] a) A. Ahmed, J. Clayden, S. A. Yasin, *Chem. Commun.* **1999**, 231-232; b) J. Clayden, F. E. Knowles, C. J. Menet, *Synlett* **2003**, 1701-1703; c) A. K. Beck, D. Seebach, G. Nikonov, *N*,*N*'-Dimethylpropyleneurea. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2012**; d) J. Clayden, F. E. Knowles, C. J. Menet, *Tetrahedron Lett.* **2003**, *44*, 3397-3400; e) J. Clayden, S. Parris, N. Cabedo, A. H. Payne, *Angew. Chem. Int. Ed.* **2008**, *47*, 5060-5062; *Angew. Chem.* **2008**, *120*, 5138-5140. f) J. Clayden, W. Farnaby, D. M. Grainger, U. Hennecke, M. Mancinelli, D. J. Tetlow, I. H. Hillier, M. A. Vincent, *J. Am. Chem. Soc.* **2009**, *131*, 3410-3411; g) A. M. Fournier, R. A. Brown, W. Farnaby, H. Miyatake-Ondozabal, J. Clayden, *Org. Lett.* **2010**, *12*, 2222-2225; h) J. Clayton, J. Clayden, *Tetrahedron Lett.* **2011**, *52*, 2436-2439.

[13] We assume from precedent [see ref 10a and M. A. Vincent, J. Maury, I. H. Hillier, J. Clayden, *Eur. J. Org. Chem.* **2015**, 953-959.] that the rearrangement is configurationally retentive. This assumption is supported by the diastereospecific rearrangement of **16d** to **17d** [see ref. 18.]

[14] M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1552-1557.

[15] In common with other medium ring nitrogen heterocycles (K. Tomooka, N. Komine, D. Fujiki, T. Nakai, S. Yanagitsuru *J. Am. Chem. Soc.* **2005**, *127*, 12182–12183) some of these compounds (**7b**, **7d**, **7h**, **7i**, **11**, **15b**, **15c**, **17c** showed exchange-broadened signals in their NMR spectra.

[16] K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740-11743.

[17] *In situ* IR and deuteration studies of the deprotonation of the related compound **7a** with either *sec*-BuLi or LDA at −78 °C allowed us to deduce that under the reaction conditions used for ring expansion no anion is formed at the doubly benzylic position adjacent to N (see SI for further details). The diastereoselectivity is thus under kinetic control and is not the result of epimerisation of the newly formed stereocenter after ring expansion. Further mechanistic studies are under way.

[18] X-ray structures and NMR data for **16d** and **17d** show that this reaction is stereosepecific and retentive. By analogy, and from ref 10a and 13, we assume this is also the case for ring expansion of **8** and **9**.

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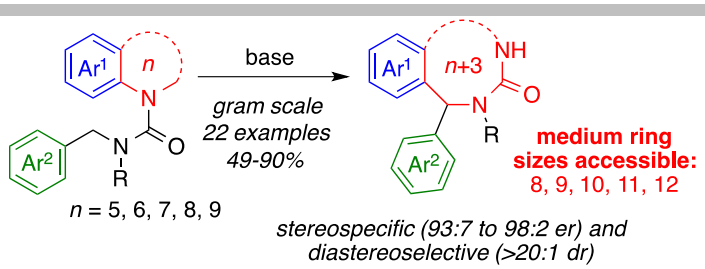


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